Cognitive Reserve, Individual Alpha Frequency in Parkinson's disease

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Abstract

Cognitive reserve (CR) may delay cognitive decline during ageing and neurodegenerative diseases. The idea has been primarily supported by studies in Alzheimer's disease (AD) where CR may maintain the cognitive abilities of patients despite AD neuropathology. Parkinson disease (PD) patients often experience significant cognitive decline and dementia, so it is possible that CR may also influence the rate of cognitive decline in this disorder. EEG metrics are associated with cognitive decline, including in PD. The current study investigated the moderating effect of CR on the relationship between the individual alpha frequency (IAF) and current cognition in PD. We examined 44 PD patients with relatively normal cognition (PDN), 40 PD patients with mild cognitive impairment (PD-MCI) and 28 healthy participants. Multiple linear regression was conducted where IAF and a proxy for CR, either years of education or premorbid IQ, were used as predictors for cognitive scores. Age and gender were used as covariates. Moderation was defined as a significant interaction term between IAF and CR in the regression. Neither years of education nor premorbid IQ moderated the relationship between IAF values and cognitive ability. Although these findings may reflect the statistical power of the study, they suggest that IAF is a relatively robust measure of brain function associated with cognition in PD that is not strongly affected by CR.

1. Introduction

Yaakov Stern (2009) proposed the cognitive reserve (CR) theory to explain the discrepancy between brain decline and corresponding cognitive decline that can occur in neurodegenerative disorders. The CR theory suggests that individuals gain more efficient brain function as a consequence of various positive life experiences. Therefore, a brain that has experienced relevant environmentally-driven improvements is better able to cope with subsequent brain decline, at least to some extent, which is exhibited by the maintenance of functions such as cognition despite evidence of neurodegeneration.

The current study investigated the potential protective effect of CR on cognitive abilities in patients with Parkinson's disease (PD) using EEG as a measure of brain changes. Specifically, years of education and premorbid IQ were used as two proxies of CR and a stable EEG measure, i.e., individual alpha frequency (IAF), was used as a proxy of brain function integrity. The aim was to examine the moderating effect of CR on the relationship between IAF and cognitive ability. If such moderation exists, it would support the idea that some of the heterogeneity that exists across PD patients may be explained by CR. While limited studies have examined the moderation effect of CR in PD, no study has examined this relationship using EEG.

1.1. Parkinson disease

PD is the second most common neurodegenerative disease after Alzheimer's disease (AD). One per cent of the population over the age of 60 is diagnosed with PD (de Lau & Breteler, 2006). The aetiology of PD is still not known. A PD diagnosis is reliant on an individual displaying characteristic motor symptoms, especially bradykinesia with decline in movement speed/amplitude overtime after movement initiation, but also classic signs of tremor or rigidity, as well as altered gait (Kalia & Lang, 2015; Postuma et al., 2015). The motor

symptoms are primarily associated with the loss of dopaminergic neurons in the substantia nigra pars compacta (Braak et al., 2003). The loss of dopaminergic neurons is associated with misfolded alpha-synuclein protein and Lewy bodies. The Braak staging described a bottom-up model of progressive neurodegeneration in PD (Braak & Del Tredici, 2017). The earliest signs of PD-related pathology in the brain is commonly detected in the olfactory bulb and the lower brain-stem, particularly the dorsal motor nucleus of the vagal nerve, but there is also pathology in the enteric nervous system (Jellinger & Jellinger, 2018). The disease pathology spreads in a superior fashion up the brain stem, reaching the substantia nigra and basal nucleus of Meynert. Once significant pathology is found in the substantia nigra, then motor symptoms emerge that characterize a motor diagnosis of PD (Hawkes, Del Tredici, & Braak, 2010).

Severe cognitive impairments also often develop in PD. These are presumed to be related to pathology in the mesocortex, allocortex and then eventually the neocortex. Dementia in PD (PDD) is a consequence of this stages (Braak & Del Tredici, 2017; Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004). Better awareness of the frequency and progression of cognitive decline has been one of the most significant changes in PD research in recent years (Goldman et al., 2018; Weintraub, Tröster, Marras, & Stebbins, 2018). In recognition of this, the current definition of PD has shifted from a motor disorder to the broader understanding that PD is a progressive neurodegenerative disease that affects multiple neural systems in the brain, not just the brain's motor systems (Baba et al., 1998; Braak & Del Tredici, 2017; Braak et al., 2003)

1.2. Cognitive impairment and dementia

Cognitive impairment has a larger impact on well-being than motor problems and significant loss of cognitive independence (i.e. PDD) associates with high co-morbidity, caregiver

burden and early mortality (Jones, 2017; Backstrom, 2018). As many as 30-50% of PD patients show neuropsychological impairments meeting criteria for PD with mild cognitive impairment (PD-MCI) (Litvan et al., 2012; Saredakis, Collins-Praino, Gutteridge, Stephan, & Keage, 2019). Patients with a PD-MCI diagnosis have a highly elevated risk of progression to dementia, which is much higher than the risk associated with advancing age or neuropsychiatric symptoms (Hoogland et al, 2017; Wood et al, 2016). While a substantial proportion (50-80%) of all PD patients eventually develop a significant loss of everyday cognitive function and independence, triggering a dementia diagnosis (PDD), the rate of cognitive decline varies across individuals affected with PD. Moreover, not all PD-MCI patients worsen and some even revert to normal cognition (PD-N) status. Such observations have been associated with environmental and person-specific factors. For example, being tired or stressed at the time of testing will influence testability (Saredakis et al., 2019). However, this is probably only a partial explanation of why there is reversion from PD-MCI to relatively normal or near-normal cognition. Similarly, despite PD-MCI being a high-risk factor for progression to PDD, we do not know why some people progress quickly while others are relatively resilient to further progression.

The range of pathophysiological mechanisms associated with progression to PDD is yet fully understood. This is partially due to uncertainty regarding the underlying neuropathology mechanisms and partly the heterogeneous nature of symptoms expressed by patients during the non-dementia period. Lewy bodies, argyrophilic inclusions, neurofibrillary tangles, senile plaques, and microvascular disease may all be contributing pathological factors in the progression to PDD (Gratwicke, Jahanshahi, & Foltynie, 2015). However, the expression of such contributing factors will differ from case to case. This matter is complicated further by examples of neuropathology that do not match prior symptoms. Autopsy studies have reported widespread α-synuclein pathology which

corresponds to the later stages of Braak's staging, yet a significant proportion of patients were not clinically demented (Burke, Dauer, & Vonsattel, 2008; Gratwicke et al., 2015; Jellinger, 2009).

As mentioned, MCI is a common feature for many if not most patients at some point in the neurodegenerative process. PD-MCI is the intermediate cognitive stage between relatively normal cognition (PD-N) and PDD. In PD-MCI, cognition is below what would be expected for the person's age, but independence and everyday functions are not significantly affected. Early detection of PD-MCI provides the opportunity to understand the progression of PD and a chance for early intervention to delay PDD onset. However, nearly 24% of PD patients may have MCI at the time of diagnosis (Guella et al., 2016), which suggests again that other factors than the pattern of neurodegeneration may influence the emergence and progression of cognitive decline in PD.

While it is logical to expect that brain decline would lead to cognitive decline, present studies still cannot accurately estimate the severity of cognitive decline based on their disease progression in the brain. Due to the lack of in vivo biomarkers for alpha-synuclein, we do not know the extent of α-synuclein pathology in patients who do not meet criteria for PDD. The situation is different in Alzheimer's disease (AD), but even for this disorder, we know that many subjects must have remained cognitively intact despite widespread β-amyloid accumulation (Guzzetti, Mancini, Caporali, Manfredi, & Daini, 2019). The mismatch of disease progression and cognitive decline has created difficulty in the search and implementation of biomarkers and complicates understanding the process of neurodegenerative disorders such as AD and PD.

1.3. Cognitive reserve

Cognitive reserve (CR) represents the adaptability of cognitive processes that have been gained through life experience such as education, social engagement, occupation and leisure activities (Yaakov Stern, 2009; Y. Stern et al., 2018). The CR hypothesis suggests that people with higher CR would have a brain that is more efficient, flexible and resilient. Thus, CR may partly account for individual differences in terms of disease resilience and protection against cognitive decline despite neuropathology. Because CR is a concept that is contributed by many factors and experience, it cannot be measured directly and so instead is represented by various proxy variables (Y. Stern et al., 2018). The generally accepted proxies are education, pre-morbid IQ, occupational complexity, leisure and physical activity. Education and pre-morbid IQ are the most popular proxy variables in CR studies (Jones et al., 2011).

Several studies have reported that more years of education and higher premorbid IQ are beneficial factors that may combat cognitive decline in PD (Hindle, Martyr, & Clare, 2014). This follows studies of normal ageing, where higher education is shown to be associated with better cognitive performance. An example of this association in PD is a study by Lee et al. (2019). They reported that higher education was positively correlated with baseline MMSE, as well as a lower risk of PD progressing past Stage 3 on the Hoehn and Yahr scale. Like AD, PD patients with higher pre-morbid IQ are also reported to have fewer cognitive impairments than people with low pre-morbid IQ (Koerts, Tucha, Lange, & Tucha, 2012; Osone, Arai, Hakamada, & Shimoda, 2015). In the absence of a marker for brain integrity, however, we do not know whether these associations reflect the specific influence of CR.

In AD, several studies reported that the rate of cognitive decline was slower when there was evidence of higher CR, despite the rate of brain deterioration (van Loenhoud et al.,

2019; Xu, Yu, Tan, & Tan, 2015). Yaakov Stern (2012) reported that people showing AD neuropathology and with less than 8 years of education were 2.2 times more likely to develop dementia than people showing AD neuropathology but more than 8 years of education. Post-mortem examinations revealed amyloid plaques deposits that would signify probable dementia in many cognitively normal older people (van Loenhoud et al., 2019; Xu et al., 2015). These findings suggest that CR may be related to better maintenance of brain function over and above the biological integrity of the brain (Yaakov Stern, 2012; Xu et al., 2015). van Loenhoud et al. (2019) found that in non-demented groups, higher CR was associated with a slower decline in memory and executive function. They also found that higher CR was negatively associated with the risk of conversion to MCI and dementia. Once dementia was reached, however, van Loenhoud et al. (2019) reported an accelerated decline in cognition in people with high CR, presumably because neural systems had become overwhelmed by the severity of neuropathology. Bruandet et al. (2008) also observed an accelerated cognitive decline with AD dementia patients that had higher education. They also reported that the mortality rate of the ADD groups was unaffected by education. These findings demonstrate that CR may no longer compensate for the decline of the brain in the advance stages of AD neuropathology and point to the importance of examining CR effects during the earlier stages of neuropathology in any disorder.

Stern et.al (2018) proposed that the optimal way to determine the protective effect of CR to examine the moderating effect of CR on the relationship between brain integrity and current cognitive ability. To test for the moderation effect of CR, a study should include 3 components; a measure of the status of the brain, a proxy measure of CR and a measure of current cognitive performance. The critical point is that the moderation effect of CR is then tested by examining the impact on current cognition of the interaction between brain measure and the proxy measure of CR. The influence of the independent effect of the proxy CR

measure alone is insufficient evidence to conclude a CR effect because this effect explicitly excludes any measure of brain function; it simply reports the unsurprising finding that more education, or a higher premorbid IQ, associates with better cognitive performance when older.

Currently, only a small number of studies have incorporated all 3 components in the manner proposed by Stern et al. (2018). A search using cognitive reserve and Parkinson as keywords yielded 95 results on Scopus and 99 results on PubMed. On closer inspection, virtually none of these studies tested for the moderation effect of CR in the context of PD. Indeed, Lucero et al. (2015) is the only study to date that has examined the interaction between CR and brain measure in the context of PD. They used β-amyloid accumulation as the brain measure and found a moderating effect of education between this brain measure and current cognition. They reported that the correlation between β-amyloid deposition and cognition was only evident for the low education group (years of education < 16). Their findings support that higher CR increases functional adaptability and cognitive 'resilience' in PD, at least with respect to the impact of amyloid pathology.

Table 1. summarizes a list of non-EEG studies that have incorporated the 3 components, as suggested by Stern et.al (2018). In general, CR has been positively associated with various aspects of cognitive and brain function. However, some of the studies did not explicitly test whether CR moderates the relationship between brain measure and cognitive ability. In one study that did do so, Artemiadis et al. (2020) investigated the effect of CR on cognitive performance in multiple sclerosis patients. Multiple regression suggested the Expanded Disability Status Scale (EDSS; Artemiadis et al. suggests that this measure can be interpreted as a biological measure that has both neurological and physical aspects) as the strongest predictor of cognition followed by CR (proxy by cognitive reserve index questionnaire, CRIq). The study also found a significant interaction term of CRIq by EDSS, where high CR

exerted a moderating role in the negative association of disability with information processing speed. In patients with late-life depression, Lin et al. (2020) found an interaction effect between education and white matter hyperintensity for category verbal fluency as an outcome variable. McKenzie et al. (2020) found a moderating effect of CR on AD biomarker, where it reduces the decline of executive function (EF) in AD patients. Using a similar database as used by McKenzie et al., Bauer, Brown, and Gold (2020) found a positive correlation between education and cognitive performance in AD patients. They also found a negative effect of AD biomarkers on cognition. However, they did not find a moderation effect of education on the relationship between AD biomarkers and cognitive performance. One thing to note is that McKenzie et al used the database of Alzheimer's Disease Neuroimaging Initiative 1 and 2, whereas Bauer et al only used Alzheimer's Disease Neuroimaging Initiative 1. Hence McKenzie et. al. used almost triple the number of subjects compared to the study by Bauer et al. (2020). Franzmeier et al. (2016) found a positive correlation between education and cognitive performance in AD patient. However, they did not examine the interaction between CR and a brain measure. In frontotemporal dementia study, Premi et al. (2020) looked at the correlation between metastate global dynamic fluidity (brain measure obtained from MRI) and education which they found to be significant. They also found that higher education patient.

with comparable clinical severity would express more global functional connectivity. They did attempt to investigate the moderation effect of CR in their study. Across different studies using the "3-variable" rule, conflicting findings have been presented for the moderating effect of CR in the literature. Further research is needed to understand the impact of CR on cognitive resilience in PD because thus far there is only one study that directly tests the possibility of CR in this condition that meets the criteria specified by Stern et al. (2018).

Table 1. Non-EEG CR studies that included a brain measure, CR measure and cognitive outcome.

Name	N	Diseases	Proxy	Method	Statistical method	Disease diagnosis method	Neuropsychological assessment	Moderation found?
Lucero et al. (2015)	155	PD	Years of education	MRI and PiB PET imaging	Multiple linear regression	UKPDSBB clinical diagnostic criteria*	CDR, MMSE	Yes
Franzmeier et al. (2016)	24 control, 43 aMCI	AD	CRIq, years of formal education	fMRI	Linear regression	Amyloid-PET positive= of global [18F] AV-45 PET standardized uptake value ratio >1.11	CERAD word list learning tests Rey Auditory Verbal Learning Test (RAVLT)	No
Premi et al. (2020)	256	FTD**	Years of education	MRI	Partial Pearson's correlation	Clinical diagnostic criteria of behavioural variant frontotemporal dementia	MMSE, Clock-Drawing Test and other various neuropsychological assessments	No
Artemiadis et al. (2020)	526	MS***	CRIq	Neuropsychological assessment	Linear regression	2011 revised McDonald Multiple sclerosis criteria	Symbol Digits Modalities Test (SDMT), California Verbal Learning Test II (CVLT-II), Brief Visuospatial Memory Test-Revised (BVMT-R), Expanded Disability Status Scale (EDSS)	Yes
Bauer et al. (2020)	441	AD	Years of education	MRI	Linear mixed models	Reported memory concern, Abnormal memory function score on Wechsler Memory Scale; Mini-Mental State Exam (MMSE) score of 20-26 (24-30 for MCI); Clinical Dementia Rating (CDR) = 0.5(MCI) or 1.0	Composite longitudinal memory and/or executive function from the original study (MMSE, etc.) Alzheimer's Disease Neuroimaging Initiative 2	No
McKenzie et al. (2020)	1214	AD	residual reserve index (see Reed, 2010)	MRI	Structural equation model	Same as above	Same as above	Yes
Lin et al. (2020)	92	WMH*** and depression	Years of education	MRI	Linear regressions	DSM-5 major depressive disorder criteria, WMH was quantified using the fuzzy connectedness segmentation algorithm on WM lesions fromT2-FLAIR images	MMSE, digit symbol substitution test (DSST), letter-number sequencing, Geriatric Depressive Scale (GDS)	No

***** *the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria; ** frontotemporal dementia Multiple sclerosis; *** White matter hyperintensity*

1.4. Electroencephalograph

The electroencephalogram (EEG) was conceptualized in the late 19th century. It was first used in sleep studies in the 1930s and its popularity has increased immensely recently. EEG has been used to address brain function and cognitive function in healthy people and many disorders (Amato, Caverzasio, & Galati, 2020). EEG is a non-invasive and low-cost method to generate information on brain activity. EEG uses electrodes on the scalp to monitor and record electrical activity generated by cortical layers of the brain, to continuously monitor brain activity with a high temporal resolution in the order of milliseconds. Because of the non-invasive, high-temporal resolution, and simple setup properties of EEG, studies can introduce stimuli more freely than methods that use large machinery such as magnetic resonance imaging (MRI) and positron emission tomography (PET) (Chaumon, Crouzet, & Busch, 2015; Wagner, Chaves, & Wolff, 2017). Therefore, EEG is a suitable choice in studies that monitor brain activity involving fragile populations such as PD and AD patients.

EEG has been robustly linked to age and disease-related brain decline (Benz et al., 2014). It is widely reported that a slowing down of EEG alpha rhythm occurs with ageing, which is accelerated with cognitive decline. During resting-state wakefulness, cognitive decline has been found to be associated with the increase of EEG power in theta and delta bands but a reduction of power in alpha and beta bands (C. Babiloni et al., 2018; Stoffers et al., 2007). In PD and AD, the slower alpha rhythm has been detected before signs of cognitive decline, suggesting EEG as a measure of brain integrity rather than a direct reflection of cognitive ability (Benz et al., 2014; Smit, Wright, Hansell, Geffen, & Martin, 2006).

The use of EEG to study CR has been limited. Table 2 summarizes studies that used EEG to investigate the effect of CR in cognitive decline. Babiloni et al. (2020) investigated

the effect of education level in presumed AD patients showing subjective memory complaints (SMC). The study tested for the moderation effect of education on SMC to predict power density, which is conceptually similar to the reverse in which cognition is the outcome variable. Power density is a measure of the amount of brain activity in a frequency band, as a representation of brain integrity. The study found that that education moderates the relationship between SMC and power density in the non-SMC group but not in SMC group. In the non-SMC group higher education was associated with higher posterior alpha power in the parietal, occipital and temporal brain region. In the SMC group, higher education was only associated partially (only in alpha 3 band instead of the whole range of alpha) in the temporal region. Babiloni et al. (2020) suggested this the inconsistency of alpha power between the two groups was due to the failure of CR, where CR's compensatory effect could not sufficiently cope with the brain decline in the SMC group.

Amodio, et al. (2017) found that cognitive decline was positively correlated with the psychometric hepatic encephalopathy score (PHES, a test for cognitive impairment) in hepatic encephalopathy patients. They found that higher CR maintain their PHES (delay cognitive decline). However, they found no association between PHES and any of the EEG measures (Mean Dominant Frequency, alpha, beta, delta, and theta power). They suggested that EEG is more reflective of neurophysiologic assessments instead of cognitive assessments. Gu et al. (2018) reported a positive correlation between CR and neural efficiency and task reaction time in Amnestic MCI patients. They defined neural efficiency as the "degree to which a task-related brain network must be activated to fulfil the task". Task-related neural processing (P300 amplitude/latency) was used to derive a neural inefficiency score (an inversed neural efficiency measure). They found a positive association between CR and neural efficiency. Fleck et al. (2017) examined the impact of age and CR on brain connectivity with healthy adults. They reported CR a reduction of the mean coherence (brain

connectivity) in younger participants and an increase of mean coherence in older participants. Fleck et al. proposed that the low mean coherence in younger participants with CR may be a result of better network efficiency and the increase in older participants may be the compensation effect. The most relevant finding in this study was the interaction effect for age and CR on brain coherence. Although not a traditional cognitive performance measure, brain connectivity has been associated with cognitive performance (Kranczioch, 2017; Vecchio et al., 2016). Therefore, the finding suggests that CR could benefit cognitive performance through the moderation of the impact of ageing.

To the best of author's knowledge, no study examined the moderation effect of CR in PD using EEG. Individual alpha frequency (IAF) is a suitable EEG brain measure derived from EEG signals. IAF is the frequency of peak power in the extended alpha band (i.e. 5-14 Hz) (Goljahani et al., 2012; Haegens, Cousijn, Wallis, Harrison, & Nobre, 2014). An individual's IAF increases from childhood to adulthood and then decreases with age. This is thought to mimic brain development and decline (Haegens et al., 2014). In twin studies, the heritability estimates of IAF is about 80% showing that IAF is strongly influenced by genetic factors (Goljahani et al., 2012; Haegens et al., 2014). With the relation to age and genetics, IAF is less likely to be a direct measure of cognitive ability but rather a direct measure of brain structural-functional integrity.

Table 2. CR studies with EEG as brain measure.

Name	N	Diseases	Proxy	Statistical method	Disease diagnosis method	neuropsychological assessment	EEG measure	Moderation found?
Babiloni et al. (2020)	318	Subjective memory complaint (SMC) with AD pathology	Education With a 1-8 scale	ANOVA	positive amyloid β deposition on 18F-florbetapir and Question relates to SMC	Mini-Mental State Examination (MMSE) score ≥ 27 and Clinical Dementia Rating score (CDR) = 0 for cognitively normal	posterior rsEEG power density at the individual alpha 2 and alpha 3 bands	Yes
Amodio, Montagnese, Spinelli, Schiff, and Mapelli (2017)	82	Hepatic encephalopathy (HE)	CRI questionnaire (CRIq)	ANCOVA	Clinical diagnose of cirrhosis	PSE syndrome test*	Mean Dominant Frequency, relative power of the theta band, the relative power of delta band	No
Gu et al. (2018)	84	Amnestic MCI	CRIq	ANCOVA and RMANOVA	MMSE ≥ 24, not dementia according to NINCDSADRDA** Alzheimer's Criteria, CRD=0.5 and verbal confirmation by patient and informant	MMSE, CDR Mattis Dementia Rating Scale-2 (MDRS-2) and other various neuropsychological assessments	Mean P300 amplitudes,	No
Fleck et al. (2017)	93	Ageing	Years of education and verbal IQ scores	ANOVA		MMSE-2, Clock Drawing Test, The National Adult Reading Test, Revised (NARTR) and other various neuropsychological assessments	Mean coherence of delta, theta, low alpha, high alpha, beta, and gamma	Yes

Psychometric Hepatic Encephalopathy Score National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association*

1.5. Aim

Thus far, the moderating effect of CR on the relationship between cognition and brain measure has been investigated in the context of PD only once and never using EEG. The current study aimed to determine the moderating effect of CR on the relationship between a stable EEG measure and cognitive ability. The individual alpha frequency (IAF) was used as a suitable EEG metric; education and premorbid IQ were used as two separate proxy measures of CR. CR proxies were expected to have significant interaction with IAF in predicting cognitive performance. That is, for similar IAF values, participants with higher education and/or premorbid IQ should have higher cognitive scores compared to those with lower CR.

2. Method

2.1. Participants

This study was based on an ongoing EEG study from New Zealand Brain Research Institute (NZBRI). The collection of EEG data was mainly done by trained colleagues at the NZBRI, especially Emma Peterson. The author is familiar with the process and collected EEG from a few participants. The author is familiar with the process and collected EEG from a few participants, although further involvement was curtailed by Covid-19 restrictions during 2020. The participants were recruited from the participant pool of an ongoing longitudinal study based at the NZBRI. Before recruitment for the current EEG study, the NZBRI cohort had already been selected. Exclusion criteria included significant psychiatric history (e.g. current diagnosis of schizophrenia, bipolar affective disorder or histories that warranted hospitalization), a significant past or current substance abuse or dependence (alcohol included), a moderate or severe traumatic brain injury, history of learning disability or suffering from a significant neurological condition that is not PD. The EEG study added

additional exclusion criteria. The participant was excluded if they had unremovable metal objects in the skull and neck area and/or a non-corrected severe sight problem (e.g. partial blindness). They were also required to have detailed neuropsychological testing within 6 months of the EEG session.

The diagnosis of the PD participants was based on the UK Parkinson's Society criteria (Hughes, Daniel, Kilford, & Lees, 1992) supplemented by MDS criteria (Postuma et al., 2015). The PD participants were classified as showing cognition in the normal range for their age (PD-N), PD with mild cognitive impairment (PD-MCI) or PD dementia (PDD), based on the Movement Disorders Society (MDS) task force level II criteria (Postuma et al., 2015). Cognitive assessment was based on an abbreviated selection of neuropsychological tests (10 tests) found by the NZBRI to provide good longitudinal (4-year) prediction of progression from PD-MCI to PDD (D. J. Myall et al., 2020). The neuropsychological tests provided 2 measures in each of 5 cognitive domains, thereby fulfilling Level II criteria for PD-MCI if two impairments existed, in our case, at -1.5SD below normative scores (Litvan et al, 2012; Table1). The PDD criteria (Dubois et al 2007) required significant impairments (-2 SD below the normative mean) in at least two cognitive domains that are causal for significantly impaired everyday cognitive function not attributed to motor impairments; in the current study, a PDD diagnosis was ascertained prior to the study but PDD status was verified closer to the EEG session using the MoCA and information from a significant other. However, very few patients with PDD were able to provide data on the 10 neuropsychological test measures and were not examined further. That is, the current study focused on PD-N and PD-MCI patients, together with healthy controls.

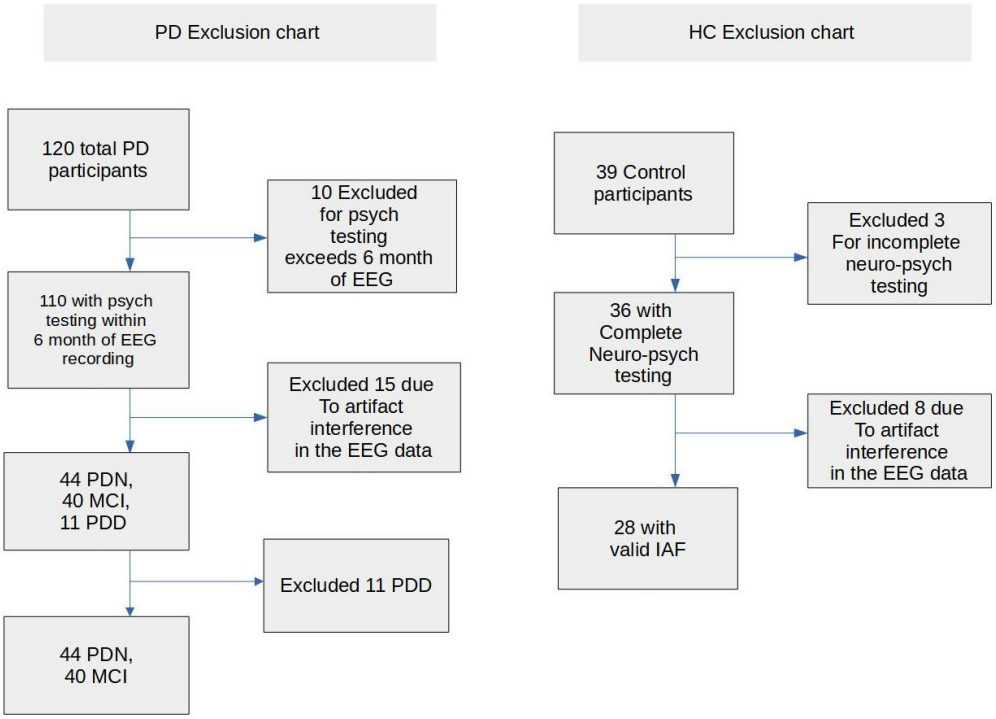

Figure 1. Exclusion process of PD and HC participant groups

A total of 163 participants, including 39 healthy controls (HC), were recruited from the NZBRI longitudinal cohort's database via phone calls from the Research Coordinator. Of those, 159 participants completed comprehensive neuropsychological testing. The PD group had 120 cases; 10 cases were excluded for not having neuropsychological testing within 6 months of the EEG session. 15 PD cases were excluded due to artefacts interference in the EEG data. Thus 95 cases remained in the PD group after exclusion, 44 PD-N, 40 MCI and 11 PDD (PDD excluded for reasons above). The HC group had 39 cases, 3 were excluded for incomplete neuro-psychological testing and 8 were excluded for to artefacts interference in the EEG data. Figure 1**.** describes the flowchart for participants.

2.2. Neuropsychological tests

The neuropsychological data were gathered by research assistants during sessions that were part of in the longitudinal study based at the NZBRI. The author did not conduct any of these

test sessions. The sessions collected demographic information, the Unified Parkinson's disease rating scale (UPDRS III), the Hoehn and Yahr stage (HY), Montreal Cognitive Assessment (MoCA), the Clinical Dementia Rating scale (CDR), and premorbid IQ using the Wechsler Test of Adult Reading (WTAR) test. Although 21 neuropsychological test measures were routinely collected, we focus here on a battery of 10 neuropsychological tests (10 tests) across five cognitive domains that have found to have the strongest predictive value for conversion to PDD within 4 years, which therefore were used to determine a determine PD-MCI status (D.J. Myall et al., 2020). The 10 tests are listed in Table 3. A global Z score of the 10 tests was calculated by averaging scores across these 10 tests. To ensure the EEG data gathered was an accurate representation of cognitive ability, participants that had not received neuropsychological tests within 6 months of the EEG session were excluded.

Table 3. The 10test neuropsychological tests across 5 cognitive domains.

Domain	Pair of Tests per Domain	
Executive Function	Trail Making part B	Stroop interference
Attention, working memory & processing speed	TEA Map Search first minute	Digit ordering
Episodic memory	CVLT-II SF total immediate recall	RCFT immediate recall
Visuo-perceptual	Judgement of line orientation	RCFT copy
Language	Mattis DRS-2: similarities	ADAS-Cog: language

2.3. EEG

2.3.1. EEG Data Acquisition

Participants attended a two-hour EEG session at the NZBRI EEG lab in Christchurch. They were asked to perform a series of conditions in front of a computer screen while their brain activity was being recorded. The EEG data were gathered using a 64-channel EEG cap (Quick-Cap, Compumedics Neuroscan) with Ag/AgCl electrodes. A Neuroscan SynAmps 2 amplifier (24 bit) was used to amplify and digitize EEG signals. The Curry 7 software (Compumedics Neuroscan) was used to record the EEG data. The gap between EEG electrodes and the scalp was filled with conductive gel. The vertical electrooculogram (VEOG) was also recorded by placing two electrodes above and below the right eye. Mastoid electrodes were placed on the right and left mastoid bones. The impedance of the electrodes was kept below 10 kΩ. EEG was collected during an eyes-closed resting-wakefulness session. Participants were asked to close their eye and relax for 9 mins while staying awake. To ensure wakefulness, the task was interrupted every 3 min and participants were asked to open their eyes. After each session, the EEG cap was cleaned and disinfected. The testing paradigm has been developed by the team from the New Zealand Brain Research Institute (NZBRI).

2.3.2. Individual alpha frequency

PrepPipeline plugin in EEGLAB was used to remove line noise and identify bad electrodes (Bigdely-Shamlo, Mullen, Kothe, Su, & Robbins, 2015; Delorme & Makeig, 2004; Delorme et al., 2011). The EEG data were then band-pass filtered between 1 and 80 Hz using a finite impulse response (FIR) zero-phase filter. Stereo-typical artefacts were minimised using infomax independent component analysis, where artefactual components were identified automatically using FASTER and ICLabel algorithms implemented in EEGLAB(Delorme,

Sejnowski, & Makeig, 2007; Nolan, Whelan, & Reilly, 2010; Pion-Tonachini, Kreutz-Delgado, & Makeig, 2019). Canonical correlation analysis blind source separation was used to minimise muscle activity on the EEG data. EEG pre-processing was followed by applying artefact subspace reconstruction (ASR) with k=5 to minimise the remainder of artefacts (Clercq, Vergult, Vanrumste, Van Paesschen, & Van Huffel, 2006; Mullen et al., 2015). Rejected electrodes were interpolated using spherical spline method in EEGLAB. Surface Laplacian was applied to remove the volume conduction (Tenke, Kayser, Abraham, Alvarenga, & Bruder, 2015). EEG processing was conducted by Dr Reza Shoorangiz.

The clean EEG data excluding the 10 seconds epoch around wakefulness checks were segmented into 2-second epochs. Epochs were removed if they were affected by any artefacts such as movement or ocular artefacts. Hanning window was applied to the epoch to avoid edge artefacts. Spectral power was calculated using fast Fourier transform (FFT) to provide the power density of scalp resting-state EEG (rsEEG) rhythms with 0.5 of frequency resolution, taken from the posterior scalp electrodes. The extended alpha range chosen was IAF 5Hz to 14Hz, where IAF was taken as the maximum power density peak within this extended alpha range.

2.4. Ethics

The current study was approved by a local ethics committee of the New Zealand Ministry of Health (ethics ref: URB/09/08/037/AM19).

2.5. Statistical analysis

Statistical analysis was performed by Tim Xie with assistance from Dr Reza Shoorangiz, using the open-source software R (V4.0.1; http://CRAN.R-project.org/doc/). Group differences of IAF were compared by a one-way ANOVA. The moderation effect of CR on the relationship between brain measure (IAF) and cognition was assessed by a series of linear

regression analyses. Each analysis was performed for each of the CR proxies (x2) and cognitive scores (x12). That is, CR proxy (education or premorbid IQ), IAF and the interaction between and IAF and CR proxy were used as the predictors of MoCA, global Z score of the 10 tests and the Z score of individual tests (see **Table 3.**). Age and gender were included in the linear models as covariates. Premorbid IQ was based on the WTAR. Effect sizes were calculated using Cohen's f.

3. Results

3.1. Demographics and group differences

Demographic information is summarized for the PD-N, PD-MCI, and HC groups (Table 4). MoCA data was education-adjusted when retrieved from the longitudinal data set, so it was reverted to the raw score. Participants had more than one WTAR (premorbid IQ) score over time, which had not been previously investigated by the NZBRI. To determine the stability of this premorbid IQ measure, Pearson correlations were performed with the obtained median of WTAR relative to the mean of WTAR ($r = 0.99$. $p<0.01$, $n =123$), and between median WTAR and the first WTAR assessment ($r = 0.98$, $p<0.01$, $n= 123$). These strong correlations indicated the robustness of WTAR scores over time. For the current study, the median score of WTAR was chosen as a proxy of CR.

Table 4. Demographics table of all participants.

	Control	PD-N	PD-MCI
Sample size	28	44	40
Male/Female	19/9	26/18	29/11
Mean age (SD)	75.68 ±7.72	68.39 ±7.25	72.33 ±6.2
Mean Symptom duration	–	9.56 ±5.64	12.85 ±6.37
Mean years of Education	13.71 ±2.48	13.23± 2.34	12.68 ±2.52
Mean WTAR (SD)	114.2±7.56	112.2 ±9.04	109 ± 8.11
Mean IAF (SD)	8.93±0.78	8.69 ±1.07	7.85 ± 1.3
Mean UPDRS (SD)	–	28.6 ±12.05	42.41 ± 12.63
Mean HY (SD)	–	2.21 ±0.47	2.56 ±0.48
Mean LEDD (SD)*	–	933 ±1229	1015 ±528.1
Mean global Z (10 tests) (SD)	0.77 ±0.41	0.17 ±0.42	-0.99 ±0.56

**L-Dope equivalents daily dosage*

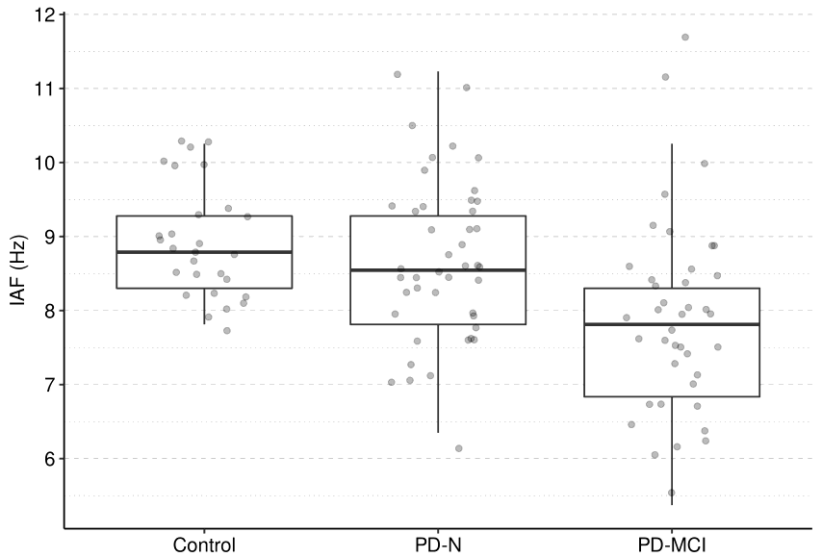

Figure 2. boxplot showing the distribution of IAF in the control, PD-N and PD-MCI groups. Points represent individual IAF of each participant; n=112.

The distribution of IAF across the three groups is described in Figure 2. ANOVA showed a significant difference in IAF among the 3 groups ($F(2,107) = 9.73$, $p<0.001$). Tukey post hoc pair-wise comparisons (Figure 3. for relative to HC group) revealed that the IAF of the control group was significantly higher than that of the PD-MCI group, but not significantly different to the PD-N group. The PD-N group's IAF values were also significantly higher than those in the PD-MCI group.

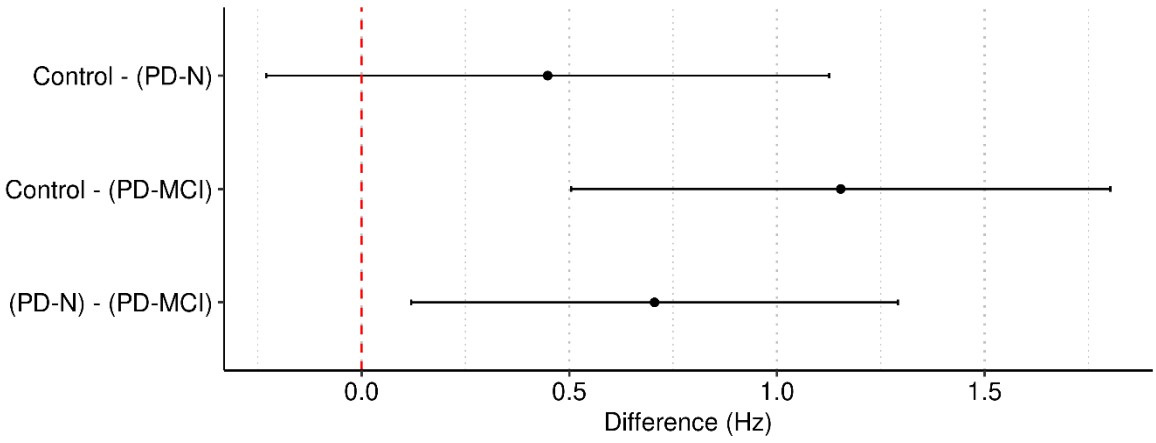

Figure 3. Pairwise comparison between control, PD-N and PD-MCI groups. Redline represents the corresponding reference group (the first group specified) relative to the comparison (the second group specified).

3.2. IAF and education as predictors of cognitive ability in the education model

When education was used as the proxy of CR, IAF was significantly associated with all cognitive measures. The largest main effect of IAF was found with TEA Map Search 1 min as the outcome (dependent) variable (β = 0.46, $p < 0.001$, f= 0.53 [0.3, 0.74]). The smallest main effect of IAF was observed for MoCA (β = 0.198, p = 0.028, f= 0.216 [0.00, 0.41]). IAF was also moderately associated with Global Z (β = 0.435, p <0.001, f= 0.478 [0.3, 0.68]) (see Table 5.)

Table 5. Main effect of IAF on cognitive scores with age and gender as covariates in the education model.

Cognitive measure	*B*	β	*t*	*p*	Cohen's *f* [CI]
Global Z score	0.311	0.435	4.805	0	0.478 [0.3, 0.68]
Trail Making part B	0.34	0.299	3.271	0.001	0.318 [0.12, 0.51]
Stroop interference	0.384	0.378	4.148	0	0.403 [0.2, 0.60]
TEA Map Search 1 min	0.46	0.463	5.36	0	0.53 [0.3, 0.74]
Digit ordering	0.278	0.237	2.514	0.013	0.245 [0.05, 0.44]
CVLT-II SF total immediate recall	0.419	0.334	3.707	0	0.361 [0.2, 0.56]
RCFT immediate recall	0.378	0.286	3.089	0.003	0.302 [0.1, 0.50]
Judgement of line orientation	0.198	0.244	2.598	0.011	0.253 [0.06, 0.45]
RCFT copy	0.353	0.33	3.654	0	0.357 [0.16, 0.55]
Mattis DRS-2: similarities	0.164	0.263	2.789	0.006	0.271 [0.08, 0.46]
ADAS-Cog: language	0.228	0.355	4.065	0	0.397 [0.2, 0.59]
MoCA	0.477	0.198	2.221	0.028	0.216 [0.00, 0.41]

Statistical significance, $p < 0.05$: IAF are significantly associated with all cognitive scores. B represents the unstandardized beta value. Note: Cohen's f interpretation: 0.14 = small, 0.39 = medium, 0.59 = large.

By contrast, years of education was not significantly associated with the Global Z score. However, years of education was found to show a weak but significant association with TEA

Map Search 1 min, CVLT-II SF total immediate recall, RCFT copy and MoCA scores (see Table 6.).

Table 6. Main effect of education on cognitive scores with age and gender as covariates.

Cognitive measure	*B*	*β*	*t*	*p*	Cohen's *f* [CI]
Global Z score	0.052	0.146	1.646	0.103	0.13 [0.0, 0.33]
Trail Making part B	0.039	0.072	0.795	0.428	0.082 [0.00, 0.27]
Stroop interference	0.048	0.098	1.095	0.276	0.104 [0.0, 0.29]
TEA Map Search 1 min	0.085	0.176	2.062	0.042	0.188 [0.0, 0.38]
Digit ordering	-0.023	-0.04	-0.43	0.668	0.055 [0.00, 0.24]
CVLT-II SF total immediate recall	0.109	0.18	2.016	0.046	0.187 [0.0, 0.38]
RCFT immediate recall	0.065	0.101	1.105	0.272	0.104 [0.0, 0.30]
Judgement of line orientation	0.069	0.176	1.902	0.06	0.181 [0.00, 0.37]
RCFT copy	0.125	0.241	2.698	0.008	0.259 [0.06, 0.45]
Mattis DRS-2: similarities	0.038	0.126	1.354	0.178	0.136 [0.00, 0.33]
ADAS-Cog: language	0.002	0.006	0.065	0.948	0.005 [0.0, 0.09]
MoCA	0.255	0.219	2.487	0.014	0.233 [0.03, 0.43]

Statistical significance, $p < 0.05$: Global Z score, TEA Map Search 1 min, CVLT-II SF total immediate recall, RCFT copy and MoCA were significantly associated with years of education. B represents the unstandardized beta value. Note: Cohen's f interpretation: 0.14 = small, 0.39 = medium, 0.59 = large.

3.3. IAF and premorbid IQ as predictors of cognitive ability in the pre-morbid IQ model

When premorbid IQ was used as the proxy of CR, IAF was again significantly associated with all cognitive measures (see Table 7.). Consistent with the education model, TEA Map Search 1 min had the largest association with IAF ($\beta = 0.469$, $p < 0.001$, $f = 0.537$ [0.3, 0.74]). Similarly, MoCA had the smallest association with IAF ($\beta = 0.22$, $p = 0.009$ $f = 0.259$ [0.06, 0.45]*)*. The association of IAF and global Z score was also moderate ($\beta = 0.445$, p <0.001, $f = 0.507$ [0.30, 0.72]).

Table 7. Main effect of IAF on cognitive scores with age and gender as covariates in the pre-morbid IQ model.

Cognitive measure	*B*	*β*	*t*	*p*	Cohen's *f* [CI]
Global Z score	0.316	0.445	5.048	0	0.507 [0.30, 0.72]
Trail Making part B	0.347	0.306	3.365	0.001	0.327 [0.13, 0.52]
Stroop interference	0.393	0.387	4.341	0	0.423 [0.2, 0.62]
TEA Map Search 1 min	0.466	0.469	5.385	0	0.537 [0.3, 0.74]
Digit ordering	0.29	0.247	2.639	0.01	0.257 [0.06, 0.45]
CVLT-II SF total immediate recall	0.436	0.348	3.901	0	0.38 [0.18, 0.58]
RCFT immediate recall	0.388	0.293	3.185	0.002	0.311 [0.1, 0.51]
Judgement of line orientation	0.211	0.26	2.846	0.005	0.276 [0.08, 0.47]
RCFT copy	0.368	0.343	3.849	0	0.376 [0.18, 0.57]
Mattis DRS-2: similarities	0.17	0.272	2.886	0.005	0.28 [0.08, 0.47]
ADAS-Cog: language	0.232	0.36	4.152	0	0.405 [0.2, 0.60]
MoCA	0.53	0.22	2.66	0.009	0.259 [0.06, 0.45]

Statistical significance, $p < 0.05$: IAF are significantly associated with all cognitive scores. B represents the unstandardized beta value. Note: Cohen's f interpretation: 0.14 = small, 0.39 = medium, 0.59 = large.

Unlike years of education, The WTAR score was significantly associated with the Global Z score. The WTAR score was also significantly associated with Stroop interference, Digit ordering, CVLT-II SF total immediate recall, Judgement of line orientation and RCFT copy and, most strongly, with MoCA (see Table 8).

Table 8. Main effect of pre-morbid IQ on cognitive scores with age and gender as covariates.

Cognitive measure	*B*	*β*	*t*	*p*	Cohen's *f* [CI]
Global Z score	0.027	0.266	3.081	0.003	0.279 [0.08, 0.48]
Trail Making part B	0.021	0.134	1.484	0.141	0.131 [0.00, 0.32]
Stroop interference	0.026	0.188	2.122	0.036	0.194 [0.0, 0.39]
TEA Map Search 1 min	0.018	0.129	2.122	0.145	0.130 [0.0, 0.32]
Digit ordering	0.032	0.197	2.131	0.035	0.201 [0.00, 0.39]
CVLT-II SF total immediate recall	0.043	0.246	2.78	0.006	0.258 [0.06, 0.45]
RCFT immediate recall	0.027	0.146	1.601	0.112	0.145 [0.0, 0.34]
Judgement of line orientation	0.033	0.293	3.236	0.002	0.302 [0.11, 0.50]
RCFT copy	0.041	0.275	3.104	0.002	0.289 [0.09, 0.48]
Mattis DRS-2: similarities	0.013	0.152	1.631	0.106	0.141 [0.00, 0.33]
ADAS-Cog: language	0.009	0.101	1.174	0.243	0.091 [0.0, 0.28]
MoCA	0.137	0.41	5.005	0.000	0.481 [0.28, 0.68]

Statistical significance, p < 0.05: Global Z, Stroop interference, Digit ordering, CVLT-II SF total immediate recall, Judgement of line orientation and RCFT copy were significantly associated with WTAR score (pre-morbid IQ). B represents the unstandardized beta value. Cohen's f interpretation: 0.14 = small, 0.39 = medium, 0.59 = large.

3.4. Moderation effect of CR on various cognitive scores

3.4.1. Education

The Moderation effect of CR on the relationship between scores of neuropsychological tests and IAF is summarized in Table 9. All analyses were adjusted for age and gender as covariates. There was no evidence of a moderating effect on education. However, the small moderating effect approached significance for Stroop interference and Digit ordering test. Importantly, similar conclusions were found when performing the same analyses with only the PD participants (i.e., without including HC). Removing the age and/or gender from the analyses did not change the results.

Figure 4. represents the interaction between years of education and IAF to estimate the Global Z. The fitted lines are derived from the statistical model to show the minimum, lower quartile, median, upper quartile, and the maximum of years of education. The graph suggests that as the years of education increases, higher IAF are more associated with the Global Z score. Therefore, the graph suggests a small trend of interaction between years of education and IAF, but the interaction effect did not approach significance.

Table 9. Moderation effect of years education on the relationship between cognition and IAF adjusted for age and gender.

Cognitive measure	*B*	*β*	*t*	*p*	Cohen's *f* [CI]
Global Z score	0.027	0.092	1.016	0.312	0.102 [0.0, 0.30]
Trail Making part B	-0.019	-0.041	-0.453	0.652	0.044 [0.00, 0.23]
Stroop interference	0.067	0.163	1.921	0.058	0.189 [0.0, 0.38]
TEA Map Search 1 min	0.021	0.05	0.555	0.58	0.054 [0.0, 0.24]
Digit ordering	0.086	0.179	1.913	0.058	0.186 [0.00, 0.38]
CVLT-II SF total immediate recall	0.067	0.131	1.46	0.147	0.142 [0.0, 0.33]
RCFT immediate recall	0.032	0.058	0.634	0.528	0.062 [0.0, 0.25]
Judgement of line orientation	0.023	0.068	0.732	0.466	0.071 [0.00, 0.26]
RCFT copy	0.029	0.065	0.726	0.469	0.071 [0.00, 0.26]
Mattis DRS-2: similarities	-0.01	-0.038	-0.403	0.688	0.039 [0.00, 0.22]
ADAS-Cog: language	0.009	0.032	0.375	0.709	0.037 [0.0, 0.22]
MoCA	0.027	0.092	1.016	0.312	0.136 [0.00, 0.33]

Results of the interaction between years of education and IAF. At the standard significance level of p = 0.05, no significant interaction was obtained across any of the cognitive scores. B represents the unstandardized beta value. Cohen's f interpretation: 0.14 = small, 0.39 = medium, 0.59 = large.

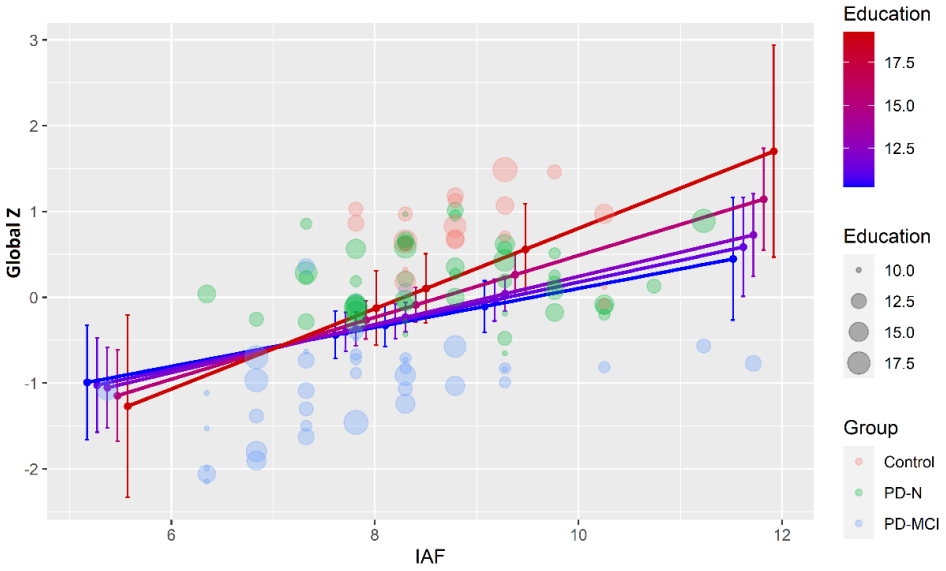

Figure 4. Interaction between years of education and IAF predicting average Z score of the cognitive 10test (global Z). Points represent raw data. Fitted lines are adjusted for gender and age derived from the model, with lines corresponding to a model-derived minimum, lower quartile, median, upper quartile, and the maximum of years of education.

3.4.2. Premorbid IQ

The moderation effect of WTAR on the relationship between IAF and cognitive scores, adjusted for age and gender, is summarized in Table 10. There was no evidence of a moderating effect of WTAR on the association between IAF and the score of cognitive tests. Only Stroop interference as the cognitive outcome suggested even a weak effect. Similar results were also obtained without adjusting for age and/or gender. The results remained non-significant after excluding the HC group. The interaction term of IAF by WTAR for the global Z score is shown in Figure 5.

Table 10. moderation effect of WTAR score on the relationship between IAF and cognitive scores, adjusted for age and gender.

Cognitive measure	*B*	*β*	*t*	*p*	*f* [CI]
Cognitive 10 test Z score	0.006	0.077	0.85	0.397	0.085 [0.00, 0.28]
Trail Making part B	0.006	0.042	0.445	0.657	0.043 [0.00, 0.23]
Stroop interference	0.02	0.168	1.855	0.066	0.183 [0.0, 0.38]
TEA Map Search 1 min	0.013	0.108	1.168	0.245	0.113 [0.0, 0.30]
Digit ordering	0.013	0.093	0.955	0.342	0.093 [0.00, 0.28]
CVLT-II SF total immediate recall	0.011	0.075	0.813	0.418	0.079 [0.00, 0.27]
RCFT immediate recall	0.007	0.044	0.457	0.648	0.045 [0.0, 0.23]
Judgement of line orientation	0.001	0.009	0.1	0.921	0.01 [0.00, 0.15]
RCFT copy	0.006	0.052	0.554	0.581	0.054 [0.00, 0.24]
Mattis DRS-2: similarities	-0.004	-0.06	-0.613	0.541	0.06 [0.00, 0.25]
ADAS-Cog: language	-0.003	-0.044	-0.489	0.626	0.048 [0.0, 0.24]
MoCA	0.022	0.077	0.896	0.372	0.087 [0.00, 0.28]

Results of the interaction between WTAR and IAF. At the standard significance level of p = 0.05, no significant interaction was obtained across any of the cognitive scores. B represents the unstandardized beta value. Cohen's f interpretation: 0.14 = small, 0.39 = medium, 0.59 = large.

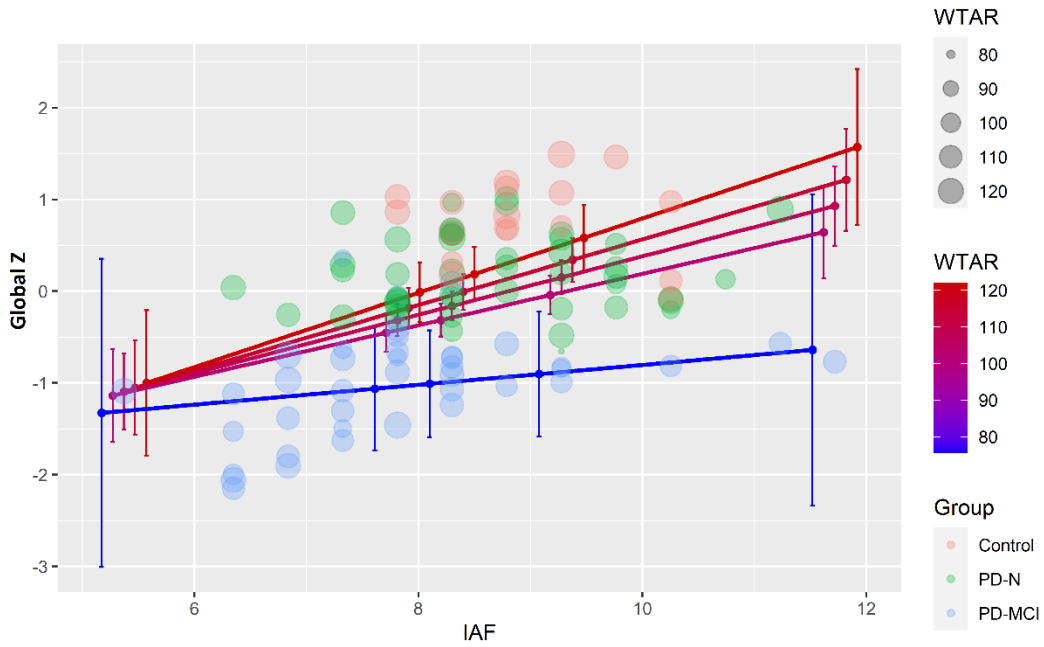

Figure 5. Interaction between WTAR and IAF predicting average Z score of the 10 cognitive tests. Points represent raw data. Fitted lines are based on the model adjusted for gender and age. The 5 lines correspond to the minimum, lower quartile, median, upper quartile, and maximum of WTAR, derived from the model.

4. Discussion

4.1. Findings

This study aimed to investigate the moderating effect of CR on the relationship between an EEG brain measure and cognition. Examining the moderating effect of CR on the association between cognition and brain integrity could help us understand the coping mechanisms of the brain when experiencing neurodegeneration and thus contribute to reasons why there is variation in cognitive decline across different PD patients. This would ultimately facilitate finding a reliable marker of cognition in PD and perhaps assist in detecting premorbid PD. However, with education and premorbid IQ the proxies of CR, there was no evidence of a moderating effect for CR on the association between IAF and scores on cognitive tests in a group of HC and PD patients. Similar results were found when the moderation effect was investigated only in the PD participants (i.e., HC excluded). The IAF differences among the 3 groups and the significant association between IAF and cognitive scores was expected; there was a decrease of IAF associated with cognitive decline (Benz et al., 2014). The lack of a moderating effect of CR on the relationship between IAF and cognitive scores suggests that CR does not have a protective effect on cognitive ability or that IAF is a specific brain measure that is resistant to the effects of CR.

Education, by itself, was not associated with the Global Z score. Some specific measures, such as TEA Map Search 1 min, CVLT-II SF total immediate recall, RCFT copy and MoCA did show weak but significant associations with education. Education has been consistently reported to be related to improved cognition since childhood and delayed cognitive decline (Bauer et al., 2020; Clouston et al., 2019). In PD studies, higher education is associated with better bassline motor and cognitive function. Higher education individuals also present a lower risk of disease progression compared to lower education individuals (Lee

et al., 2019). However, longer education does not necessarily equate to a CR effect per se in that there is no differential effect of high or low education with respect to EEG IAF as a brain measure using the criteria of Stern et al. (Y. Stern et al., 2018). Many of the previous studies suggesting a CR effect in PD only looked at the simple association between education and cognition without considering brain metrics. With the current study focusing on the cognitive impairment aspect of PD, different levels of education would maintain different levels of cognition but irrespective of brain decline relevant to non-dementia in PD.

Pre-morbid IQ had a significant relationship with the global Z score based on the 10 neuropsychological test measures. It was also associated with most of the cognitive domains except language. Although they are not the same, the relationship between pre-morbid IQ and cognitive abilities is to be expected. The inconsistency in the current research is the language domain. Like other cognitive domains, previous research has provided evidence the language is associated with premorbid (Mohn, Sundet, & Rund, 2014; Schretlen, Buffington, Meyer, & Pearlson, 2005). This lack of association may be a result of the study cohort or the specific language measures employed in our study.

4.2. Potential caveats and implications

EEG is not a brain structural measure. Evidence has suggested the protective effect of CR is expressed in compensatory mechanisms where it would cause certain regions of the brain to process information more efficiently and thus compensate for the effects of mild to moderate levels of pathology. Brain activity may decrease in damaged regions but increase in other less damaged regions or remaining local functional circuits may compensate for the loss of neurons within a region (Yaakov Stern, Barnes, Grady, Jones, & Raz, 2019). The lack of a CR effect with respect to IAF may mean that IAF is a robust measure of cognition that is independent of any CR. Although there was no significant moderation detected in the current

study the interaction between education and IAF was approaching significance for the Stroop interference and Digit ordering task. The interaction between pre-morbid IQ and IAF was also approaching significance for Stroop interference. These interaction effects were, however, small in terms of effect size. It is possible that these effects would become significant if we had a larger sample size, but they suggest that any such effects are likely to be small.

4.3. Limitations

To the best of author's knowledge, this study is the first to use EEG to examine CR and its moderation effect in the context of the PD and only the fifth study to examine CR in the context of EEG across any conditions. Several limitations and improvements need mention. Perhaps the most important is the quality of the CR proxy. Although education is the most commonly used CR proxy, its implementation and influence are variable. Education has shown to be beneficial to cognitive ability in some studies but not in others (Bauer et al., 2020; Premi et al., 2020). Education can be transformed into scales, dichotomised or as a continuous variable in the case of the current study. The way education was presented as a CR proxy should be evaluated. some studies suggest that the effect of education can only be in effect when a certain amount of educational attainment have been achieved. For example, the protective effect of Lucero et al. (2015) only present in people with 16 or more years of education, so a non-linear evaluation of years of education may be warranted. Their findings suggested that a person needs at least a university degree for education to have a CR influence. Given the average years of education in our database to be around 13 years, it is possible that education in our case did not have the effect of CR because a dichotomy using very high vs not very high years of education should be used. However, we would need a much larger sample size to test this prediction.

Nonetheless, education and premorbid IQ are proxies of CR and may not capture all aspects of CR (Y. Stern et al., 2018). Other CR contributing factors, such as lifestyle and work experience, could be substantially relevant and in some case have a greater influence than education or pre-morbid IQ. A better test of CR may require a composite measure derived from different sources. An interesting example of a composite measure is CRIq (Nucci, Mapelli, & Mondini, 2012). CRIq incorporates factors that are related to education, working activity and leisure time. Evidence has suggested that CRIq has a better correlated with cognitive impairment and motor dysfunction in PD (Guzzetti et al., 2019).

IAF is a functional measure of brain activity. Babiloni et al. (2020) found that in AD patients, high education may cause abnormal resting-state posterior EEG alpha rhythms in the parietal, occipital and temporal regions of the brain, but there was no effect of education on the alpha power across the brain. Since the moderating effect of CR may appear in certain regions, the analysis could be improved by including different regions. We have evidence that IAF in the posterior brain is highly correlated (>0.9) with alpha activity elsewhere, but CR specifically may still show regional effects.

The underlying mechanisms of CR are still unclear. Although the current study has yielded no evidence of the moderation effect of CR on the brain, future research could consider studies based on other EEG measures and other brain measures. Previous studies have suggested that the moderating effect of CR may appear compensatory, so further studies are needed to explain any compensation effects (Babiloni et al., 2020; Fleck et al., 2017; Premi et al., 2020).

5. Conclusion

This study is the first study using EEG to investigate the moderating effect of CR in PD. The results highlighted the association between IAF and cognitive abilities. However, there was no evidence of a moderating effect of CR when IAF was used as the measure of brain integrity and either years of education or pre-morbid IQ were used as proxy measures for CR. This study suggests that IAF can be considered a robust marker of cognition, which is not affected by CR and is therefore well-suited as a potential biomarker for cognition in PD.

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